REMARKS/ARGUMENTS

The Invention

The invention pertains to a composition comprising an interluekin-2 receptor associated polypeptide (ILRAP), wherein the polypeptide is capable of forming a complex with the monoclonal antibody produced by the hybridoma PTA-82, and methods of purifying the same.

The Pending Claims

Claims 1, 3, 5, 9, 11-15, 23, and 26-29 are pending. Claims 1, 3, 5, 23, and 26-29 are directed to compositions comprising interleukin-2 receptor associated polypeptides, which are capable of forming a complex with monoclonal antibodies produced by the hybridoma PTA-82, wherein said interleukin-2 receptor associated polypeptides are expressed by cells selected from the group consisting of Kit-225 cells and YT cells. Claims 9 and 11-15 are directed to methods of purifying said interleukin-2 receptor associated polypeptides. As reflected in the Amendments to the Claims, claim 9 has been amended to clarify the molecular weights of the recited ILRAPs. The amended claim is supported throughout the Specification as filed, e.g., at page 39, lines 11-25. No new matter has been added.

Applicants thank the Examiner for noting the inaccuracy of the status identifier for claim 9 provided in the previous response, filed on June 15, 2007. In view of the amendment herein, the "Currently Amended" status identifier for claim 9 is now accurate.

Discussion of Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 5, 9, 11-15, 23 and 26-29 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the reason of record set forth in the Office Action mailed on June 6, 2006 ("the June 6, 2006 Office Action"), and the Advisory action mailed November 1, 2006 ("the Advisory Action"). Additionally, the current Office Action sets forth new reasons with respect to claim 9 and its dependent claims. Applicants respectfully traverse.

The June 16, 2006 Office Action and the November 1, 2006 Advisory Action contend that since (i) Exhibit 3, submitted with the March 17, 2006 Declaration under 37 C.F.R. §

1.132 ("the March 2006 Waldmann Declaration"), indicates that pre-clearing cell lysates with anti-Tac antibody does not remove the claimed interleukin associated polypeptides (ILRAPs) and (ii) anti-Tac antibody binds to IL-2 receptor, therefore, according to the Office, the presence of the claimed ILRAPs following pre-clearing with anti-Tac antibody indicates that the claimed ILRAPs do not associate with IL-2 receptor (IL-2R). In this regard, the Advisory Action states, "*it is not explainable* that 5F7 antibody able to co-precipitate the IL-2R...but the reverse is not true, i.e., anti-Tac is not able to co-precipitate ILRAPs" (November 1, 2006 Advisory Action, page 2, second full paragraph, emphasis added). Applicants respectfully submit that this contention is incorrect for the following reasons.

The contention depends on the untenable assumption that IL-2R binding interactions are somehow transitive. The Office assumes that if anti-Tac binds IL-2R and ILRAP associates with IL-2R, then an IP with anti-Tac must co-IP all ILRAPs. As a general matter, such an assumption is not sound. Generally, a monoclonal antibody (such as anti-Tac) has a relatively high affinity for its antigen. This affinity is typically stronger than the majority of other protein-protein binding interactions involving the same antigen. Consequently, it should be expected that under immunoprecipitating conditions, antibody-antigen interactions (such as anti-Tac/IL-2R) will be more robust than other protein-protein interactions (such as ILRAP/IL-2R) involving the same antigen. Accordingly, it is unrealistic to assume, as the Office does, that all binding interactions involving an antigen are somehow transitive and that, consequently, any time an antibody-antigen complex is pulled down, the pulled down complex should also include every protein associated with the antigen to a similar extent. Without this unsound assumption, the Office has provided no basis for contradicting Applicants actual data showing that using anti-Tac to pull down IL-2R, does not pull down enough (if any) of the claimed ILRAP so as to be identifiable by SDS-PAGE (the March 2006 Waldmann Declaration, Exhibit 3).

Furthermore, the Specification and all data provided by Applicants consistently indicate that the pool of IL-2R pulled down with anti-Tac antibody is much larger than the pool of IL-2R pulled down with 5F7 antibody. For example, the 55 kDa band in lane 2 (IL-2R pulled down with anti-Tac IP) is much larger than that in lane 3 (IL-2R pulled down by co-IP with 5F7) of Exhibit 3 in the March 2006 Waldmann Declaration. The Specification also states that extended exposure was required to visualize the 55 kDa polypeptide band in

Fig. 4 (Specification, page 8, lines 1-4). Thus, Applicants data consistently indicate (a) that anti-Tac/IL-2R interactions are more robust under IP conditions than ILRAP/IL-2R interactions and/or (b) that anti-Tac and ILRAPs predominantly interact with different pools of IL-2R, respectively (and that the latter pool is smaller). In either case, the amount of IL-2R interacting with ILRAP (under IP conditions) represents only a fraction of the total amount of IL-2R that can be pulled down using the anti-Tac monoclonal antibody, which was specifically raised against IL-2R. Therefore, contrary to what is stated in the Advisory Action, the absence of ILRAP in lane 2 of Exhibit 3 is readily explainable: the amount of IL-2R interacting with ILRAP (under IP conditions) is so much smaller than the total amount of IL-2R pulled down with anti-Tac, that immunoprecipitation of IL-2R with anti-Tac did not co-IP enough of the claimed ILRAPs to be visualized in the SDS-PAGE of Exhibit 3.

The Advisory Action also alleges about Exhibit 3, "it is clear that the '55 kDa band' is non-specific. Further, there is no direct evidence in the Specification showing the direct association between the claimed ILRAPs and the IL-2R" (November 1, 2006 Advisory Action, page 2, second full paragraph). The Specification, however, directly contradicts this allegation. The Specification reports that when Applicants pre-cleared cell lysates with anti-Tac conjugated beads, the 55 kDa band that co-immunoprecipitated with the claimed ILRAPs in Fig. 4 was reduced and no longer visible (Specification, page 8, lines 6-9). Accordingly, assuming *arguendo*, even if some of the 55 kDa band in Exhibit 3 were attributable to a non-specific protein, the Office has not contradicted the direct evidence in Applicants' Specification that some, if not all, of the 55 kDa can be depleted using anti-Tac. Thus, Applicants respectfully submit that the Specification provides uncontradicted direct evidence that some, if not all, the 55 kDa band represents IL-2R.

Additionally, the Specification provides ample additional evidence demonstrating the association of the claimed ILRAPs and IL-2R. For example, Example 5 of the Specification reports that addition of IL-2 caused ILRAP to be internalized with IL-2Rβ in Kit-225 cells at 37 °C (Specification, page 33, line 11-21; and page 38, lines 5-17). In contrast, ILRAP levels did not change when IL-2 was added to Kit-225 cells at 4 °C, a temperature at which IL-2R internalization is blocked (Specification, page 38, lines 5-17). Example 6 of the Specification reports that flow cytometric resonance energy transfer (FRET) verified that ILRAP and IL-

2Rα are non-randomly associated on the surface of T-cell lines (Specification, page 39, lines 3-5, and Figure 5).

In view of the considerations presented herein, Exhibit 3 in the March 2006 Waldmann Declaration is not "opposing evidence" as alleged by the Office (June 6, 2006 Office Action, sentence bridging pages 6 and 7 and November 1, 2006 Advisory Action, second full paragraph, last sentence). Thus, given the absence of opposing evidence, the Office has not contradicted the enabling guidance in the Specification which would allow the ordinary skilled artisan to determine if a putative ILRAP associates with IL-2R.

Claim 9 and its dependent claims have been rejected as allegedly encompassing unknown ILRAPs and not being enabled. Although Applicants disagree with the rejection, claim 9 has been amended to expedite allowance of the claims. As amended, claim 9 recites an ILRAP with molecular weight of about 32,000 to 34,000 daltons or about 26,000 to 28,000 daltons as determined by SDS-PAGE. Such ILRAPs are plainly disclosed throughout the Specification (e.g., at page 3, lines 12-14, and page 39, lines 11-25).

In view of the reasons presented herein, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, as to claims 1, 3, 5, 9, 11-15, 23 and 26-29.

Discussion of Rejection under 35 U.S.C. §§ 102(b) or 103(a)

Claims 1, 3, 5, 9, 11-15, 23 and 26-29 remain rejected under 35 U.S.C. § 102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Colamonici et al., *J. Immunol.*, 145:155-160 (1990) ("Colamonici"), for the same reasons set forth in the previous Office Actions mailed June 3, 2004, April 19, 2005, October 18, 2005, June 16, 2006, and November 1, 2006. Applicants respectfully traverse.

The Office Actions mailed on June 3, 2004, and April 19, 2005, characterize Colamonici as disclosing two bands corresponding to polypeptides with molecular weights of 37 and 20 kDa, which were co-immunoprecipitated from Hut-102 cells using anti-Tac or 7G7/B6 antibodies directed to IL-2R. Although Colamonici discloses antibodies and molecular weights that differ from those recited in the claims, nonetheless, the Office Actions

assert that the burden should shift to Applicants to provide evidence that the claimed peptides differ from those disclosed in Colamonici.

On June 17, 2005, Applicants submitted a Declaration by Dr. Thomas A. Waldmann ("the first Waldmann Declaration"), which provides evidence that pre-clearing cell extracts with anti-Tac antibody does not remove the claimed ILRAPs and that the claimed ILRAPs are present in cells that do not include the antigen for anti-Tac and 7G7/B6.

The Office Action mailed October 18, 2005 characterizes the first Waldmann Declaration as insufficient. According to the Office, Colamonici does not teach that anti-Tac binds directly to the 37 and 20 kDa polypeptides and, therefore, pre-clearing with anti-Tac would only clear those 37 and 20 kDa polypeptides associated with IL-2R without necessarily clearing those polypeptides not associated with IL-2R. The Office Action further indicates that evidence using cells other than those disclosed in Colamonici would be objectionable. Additionally, the Office Action alleges that, although Colamonici discloses molecular weights that differ from those recited in the pending claims, the differences "*can be* easily explained by variations in gel concentration and running time for SDS-PAGE "in the absence of evidence to the contrary" (page 6, first paragraph, emphasis added).

On March 17, 2006, Applicants submitted the March 2006 Waldmann Declaration (discussed above), which specifically addresses the Examiner's concern regarding variations in SDS-PAGE and cells. Item 6 and Exhibit 1 compare material co-immunoprecipitated from MT-1 cells using the Applicants' 5F7 antibody and Colamonici's anti-Tac antibody, respectively. Exhibit 1 to the March 2006 Waldmann Declaration shows that the polypeptide precipitated using 5F7 (lane 2) migrates below the 37 kDa polypeptide precipitated using anti-Tac (lane 3). Since this analysis was done in the same SDS-PAGE gel, the observed difference in migration cannot be attributed to variations in gel concentrations and running time. Nor can the difference be attributed to the MT-1 cell line, since Colamonici specifically reports that the relevant 37 and 20 kDa polypeptides were precipitated from MT-1 cells using anti-Tac (page 159, second column, second paragraph). Accordingly, the March 2006 Waldmann Declaration establishes that there is a size difference between the claimed polypeptide and that disclosed in Colamonici.

The June 16, 2006, Office Action and November 1, 2006, Advisory Action dismiss the actual experimental evidence regarding size difference in the March 2006 Waldmann Declaration based on the following:

> the rejection is based on Colamonici's teachings of Hut-102 cells, not MT-1 cells as the presently claimed polypeptides are from Hut-102 cells or Kit-225 cells. Although Colamonici teaches that the 37 and 20 kDa bands also appeared in MT-1 cells, it is unclear if they are the same molecules as that in 102 cells, which are also disclosed by Colamonici.... Merely the same MW does not automatically indicate that they are the same molecules, especially given ... different cell sources."

(June 16, 2006, Office Action, page 3, second paragraph). The premise of the Office's prior art rejection is based on the disclosure of 37 and 20 kDa bands, which *differ* from the claimed MW. Thus, the Office has taken the position that this *difference* in MW is, nonetheless, close enough to evidence sameness. In the passage quoted above, the Office takes the clearly inconsistent position that, in Colamonici, the *same* MW *does not* evidence sameness merely because the bands come from different cell sources. In taking the latter position, the Office completely ignores Colamonici's disclosure that the 37 and 20 kDa bands in HUT-102 cells and in MT-1 cells were each obtained in the same way, i.e., by surface labeling with ^{125}I-rIL-2 and co-immunoprecipitating with specific IL-2R antibodies (page 159, second column, second paragraph). Thus, the sameness of the bands disclosed in Colamonici is not based "merely" on the same MW, their sameness is also evidenced by their having the same cellular and immunochemical properties. The Office has not provided any evidence that specifically contradicts Colamonici's teachings that the 37 and 20 kDa bands in MT-1 and HUT-102 cells, which have the same size and same cellular and immunochemical properties, are the same.

In the absence of evidence contradicting Colamonici's teachings that the 37 and 20 kDa bands in MT-1 and HUT-102 cells are the same, the Office has no basis for stating, "it is unclear if they are the same molecules." Their sameness is explicitly taught by Colamonici, and cannot be refuted by unsupported speculation.

In the June 16, 2006, Office Action, the Office cites the Colamonici disclosure that ICAM-1 has a similar MW to the γ-subunit of IL-2R (although they are different molecules) as calling into question the Colamonici disclosure that the 37 and 20 kDa bands from MT-1 and HUT-102 cells are the same polypeptides (June 16, 2006, Office Action, page 3, second

paragraph). Applicants respectfully disagree with the suggestion that the Colamonici reference contradicts its own disclosure regarding the 37 and 20 kDa bands. The disclosure cited by the Office is clearly limited to ICAM-1 and the γ-subunit of IL-2R. The cited disclosure has nothing to do with the sameness of the 37 and 20 kDa bands in MT-1 and HUT-102 cells.

For completeness, Applicants note that the Colamonici discussion regarding the difference between the 95 kDa ICAM-1 and the 95-110 kDa γ-subunit of IL-2R is not "opposing evidence" to the March 2006 Waldmann Declaration. In fact, Colamonici reports that the authors established the difference between the 95 kDa ICAM-1 and the 95-110 kDa γ-subunit of IL-2R in two ways. The first way included immunoprecipitating the polypeptides and then running them side by side on a single SDS-PAGE gel. Colamonici reports that "the size of this [ICAM-1] band is slightly different from the [95-110 band]" (page 158, second column). Thus, Colamonici actually contradicts the Office's suggestion that differences of 10% by SDS-PAGE should not be considered significant (November 1, 2006 Advisory Action page 2, last paragraph). The second way the authors established a difference between the polypeptides included the use of flow cytometry to show that ICAM-1 was absent in cells that express the 95-110 kDa γ-subunit. These are the same techniques Applicants have used to establish that there is a difference between the claimed polypeptides and those cited by the Office (see, e.g., items 6 and 9 of the March 2006 Waldmann Declaration). Therefore, contrary to what is suggested by the Office, Colamonici's discussion of ICAM-1 actually endorses the types of evidence provided by Applicants and indicates that persons of skill in the art would have considered what Applicants have provided to be convincing evidence that the claimed polypeptides differ from those in the prior art.

The June 16, 2006 Office Action also makes the completely unsupported assertion that the radio-immunoassay of Colamonici is more sensitive than the fluorescence flow cytometry method of Exhibit 4 of the March 2006 Waldmann Declaration. The Colamonici radio-immunoassay is limited to detecting ILRAPs indirectly, namely by co-IP with anti-IL-2R antibodies. The fluorescence assay in Exhibit 4, however, uses an antibody that specifically binds to the claimed ILRAPs. Therefore, a skilled artisan would expect that, whereas the Colamonici assay can only identify ILRAPs indirectly by their ability to co-IP

with IL-2R, the assay in Exhibit 4 is based on a more specific and sensitive binding reaction to the claimed ILRAPs. Accordingly, the Office has provided no reason for doubting that the assay of Exhibit 4 is as reliable as Colamonici, if not more so, for detecting the presence of the claimed ILRAPs.

The June 16, 2006 Office Action also makes the completely unsupported assertion that Colamonici discloses that MLA-144 cells were "stimulated with IL-2, which could have changed the kinetics/abundance of the IL-2R and/or associated molecules, resulting in difference detection." Colamonici does not mention stimulating with IL-2 anywhere. Colamonici discloses the *labeling* of intact cells by incubating with ^{125}I-rIL-2 at 4 °C (page 155, second column, third full paragraph). Such labeling is not stimulating.

Moreover, stimulating with IL-2R would not contradict Applicants evidence. It is well known that IL-2 binding to IL-2R actually *decreases* the abundance of IL-2R and its associated proteins on the cell surface (due to endocytic internalization of the IL-2R complex). Thus, for example, the present Specification teaches that IL-2 binding *reduces* cell surface expression of both IL-2R and the claimed ILRAPs (page 38, lines 8-17). Accordingly, even if one were to accept the Office's unsupported speculation that MLA-144 cells in Colamonici were stimulated with IL-2, a person of skill in the art would, if anything, expect that the MLA-144 cells in Exhibit 4 of the March 2006 Waldmann Declaration should have *more* cell surface 37 kDa polypeptide than what is disclosed in Colamonici. Thus, accepting the Office's unsupported contention only magnifies the significance of Applicants' data showing that the 5F7 antibody, which recognizes the claimed polypeptides, does not recognize the prior art 37 and 20 kDa polypeptides, which Colamonici specifically teaches is found on MLA-144 cells. In any case, the Office's unsupported speculations regarding IL-2R stimulation are entirely inadequate for contradicting the significance of the flow cytometry data in Exhibit 4 of the March 2006 Waldmann Declaration.

The present Office Action, dated August 23, 2007, does not raise a basis for a prior art rejection under 35 U.S.C. §§ 102(b) or 103(a) that materially differs from those already discussed above. The Office states that since "the examiner is unable to determine whether the prior art disclosure possesses the unrecited characteristics or property...then the burden shifts to Applicants to *provide evidence* that the prior art would neither anticipate nor render

obvious the claimed invention." (August 23, 2007 Office Action, paragraph bridging pages 4-5). Applicants respectfully submit that they have provided the requested evidence by way of the Colamonici reference itself and the March 2006 Waldmann Declaration, which demonstrates that the presently claimed ILRAPs differ from the molecules at 37 and 20 kDa disclosed in Colamonici.

More particularly as discussed above, Applicants have shown that the claimed polypeptide differs from the prior art in terms of MW. As discussed above, the difference was established in the same cells as taught by the prior art and the difference was observed in the same gel. The only remaining reason offered by the Office for why the difference "could be" an artifact, relates to differences in amount of polypeptide loaded in lanes 2 and 3 of Exhibit 1 in the March 2006 Waldmann Declaration. However, Applicants respectfully submit that Colamonici Figure 4B (Colamonici, page 158) shows a significant difference in the amounts of 37 kDa polypeptide (running at about 52 kDa due to IL-2R) loaded in lanes 17A1 and 7G7B6, respectively, for MT-1 cells (which are the same as those used in Exhibit 1 of the March 2006 Waldmann Declaration). Despite the difference in loading, the 37 kDa polypeptide in Fig. 4B runs at the same MW. Accordingly, the only reason for dismissing Applicants' evidence that the claimed polypeptide has a different MW form that disclosed in Colamonici is based purely on speculation.

Furthermore, the Office is clearly incorrect when it states that the claimed ILRAPS and those in the prior art are found in the same cells. The prior art (Colamonici) explicitly teaches that the 37 and 20 kDa bands cited by the Office were found on the surface of MLA-144 cells. Applicants have provided flow cytometry data using an antibody that is *specific* to the claimed polypeptides, as discussed above. The flow cytometry data in Exhibit 4 of the March 2006 Waldmann Declaration unambiguously indicates that the presently claimed polypeptides are absent from the cell surface of MLA-144 cells. Thus, Applicants respectfully submit that they have established that the claimed polypeptides differ from the 37 and 20 kDa bands taught in Colamonici.

For the reasons presented herein, Applicants respectfully submit that the prior art does not disclose (either alone or in any combination identified by the Office) each and every

element of the claimed polypeptides. Therefore, Applicants respectfully request withdrawal of the present rejection under 35 U.S.C. §§ 102(b) or 103(a).

Conclusion

In view of the foregoing reasons, this application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

Date: December 21, 2007

Bruce M. Gagala, Reg. No. 28,844
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6731
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)